the increasingly well-recognized disparity between tests of pulmonary function and *functionality* of the patient.

Many physicians have seen patients in whom bronchodilator aerosols were not effective when delivered by hand or compressor-driven nebulizers, who then benefited by the same medications administered by IPPB. Admittedly, many of these patients may have been poorly trained in the use of more simple aerosol generators, and the question of "psychological dependence" on the IPPB devices themselves certainly arises.

Adverse effects of IPPB therapy doubtless exist. A recent report supports our experience that some persons with particularly irritable airways (such as asthmatics) might respond to air under pressure with *increased* airways resistance, especially when no bronchodilators are used in the aerosol.

Over-utilization of IPPB in hospitals is a problem under increasing scrutiny by third party payers. In a recent review of 200 respiratory patient stays in our own hospital, where automatic IPPB stop orders are instituted after 72 hours, IPPB charges account for less than 10 percent of total hospital charges.

At present, a confusing and often contradictory literature notwithstanding, judicious and skilled use of IPPB in certain situations still seems to have merit, since the day when a truly controlled study of selected patients under therapy in hospitals, with and without such devices, seems a long way off. Such clinical investigation is urgently needed in light of increasing IPPB use in the hospital setting.

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Flucytosine, A Major Antifungal Agent

FLUCYTOSINE, marketed as Ancoban® (Roche), is the first new antifungal agent released to the profession in 15 years. While clinical usefulness has been limited to infections caused by cryptococcus neoformans and systemic candidiasis, the drug has established itself as a co-equal with amphotericin-B in these conditions. Its relatively low toxicity, administration by the oral route, and high sera and tissue levels, including the cerebral spinal fluid, make this an important addition to the armamentarium of the treatment of these mycoses, particularly in patients where amphotericin cannot be used.

The action of this antimetabolite, a derivative of cytosine, appears to be selective interference with metabolic pathways in certain microorganisms. Observed toxicity has included neutropenia, thrombocytopenia, and dose-related hepatic dysfunction. These have all been mild and reversible. Resistance to the organism has been seen to emerge, especially when smaller doses have been used.

Combined or alternating courses of therapy with amphotericin-B appear promising and are under investigation.

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Alpha$_1$-Antitrypsin: What's in It for the Patient?

CURRENTLY THERE IS NO WAY to arrest the progress of emphysema in patients who are deficient in alpha$_1$-antitrypsin. People who are homozygotes for the "zz" deficiency genes tend to get emphysema at an early age. While the exact incidence of emphysema in homozygotes is unknown, 95 percent of those who are found by proband studies or by referral from other physicians eventually develop emphysema. The average age of onset is about 35 years and in one large study 90 percent showed clinical effects of the disease by age 50. Once the disease has started it often pursues a relentless downhill course characterized by dyspnea and variable amounts of cough. Expiratory flow limitation can be accounted for by loss of lung elastic recoil in about half of the patients; in the other patients, airflow limitation is due to both loss of lung elastic recoil and intrinsic airway disease. Clinical evidence of chronic bronchitis does not serve as a useful predictor of the pattern of airway obstruction.

The evidence that emphysema occurs with increased frequency in heterozygotes is controversial, and the question cannot be settled from the available literature. Some observers have suggested that cigarette smoke or other pulmonary irritants may be important factors in the speed and severity of

development of the disease in heterozygotes and homozygotes but these suggestions are unproven.

In light of our limited knowledge, all we can offer these patients at present is genetic counseling, advice about elimination of irritants, and the usual therapy of emphysema. However, studies on the biochemistry of alpha$_1$-antitrypsin offer some hope that it may be possible to design a drug to replace the missing protein. With some luck such a drug may prevent the emphysema which develops in these patients.

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Hypoxemic, Hyperventilatory Respiratory Insufficiency:

A Common Post-operative Complication

WITH THE ADVENT of modern surgical techniques the morbidity and mortality associated with the intra-operative period has considerably declined. The post-operative period, however, is still fraught with many and diverse hazards, not the least of which is a fairly recently appreciated entity—hypoxemic, hyperventilatory respiratory failure. By definition this condition is associated with a PaO_2 below 60 mm of mercury, a $PaCO_2$ below 35 mm of mercury and a variable arterial pH. No patients or types of operation are immune. The etiology is multifactorial and may include one or a combination of the following: (1) Excessive intravenous fluid administration, (2) microscopic pulmonary emboli of clotted material or fat, (3) excessive supplemental oxygenation without ample humidification, (4) atelectasis, (5) anesthesia, (6) respiratory infections, (7) shock and (8) aspiration. These varied insults find expression at the pulmonary level as: mucociliary dysfunction; surfactant loss; macrophage disintegration; alveolar fluid filling and collapse; fluid and protein deposition in the alveolar capillary interstitium; and abnormal capillary blood flow and distribution. The physiologic expressions of these anatomical abnormalities are an abnormal distribution of both ventilation and perfusion, a decrease in lung compliance, an increase in airway resistance and a pronounced increase in the work of breathing—all manifested clinically as tachypnea, decreased tidal volume, hypoxemia, hypocapnia and a variable arterial pH.

Since this type of respiratory insufficiency has multiple causes, it would seem easier to prevent their occurrence than to correct them after the fact. This being so, *anticipatory* and *prophylactic* treatment would seem indicated. Thus, fluid and electrolytes should be carefully monitored particularly with an eye to preventing excess fluid loads; operative ventilatory support should not lead to under-ventilation or over-ventilation; anesthesia should be properly selected and carefully used; well humidified oxygenation should be appropriate to the patient's clinical situation; relief of pain should be accomplished with the least possible amount of analgesic, and pulmonary toilet and intermittent positive pressure breathing should be employed early and frequently. The patient's clinical condition should be followed at least daily by bedside tidal volumes and vital capacities, respiratory rates, physical examinations and arterial blood gases. If all these means are employed, hypoxemic hypocapnic ventilatory failure should decrease in frequency.

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Early Diagnosis of Chronic Obstructive Pulmonary Disease

SINCE THE ADVANCED STAGE of the chronic obstructive pulmonary diseases (emphysema, chronic bronchitis, chronic asthma, rarely, bronchiectasis) appears to follow a relentless and progressive course regardless of treatment, increasing attention has been directed to early detection. Efforts are under way to screen large populations for alpha$_1$-antitrypsin deficiency to detect high-risk individuals. Other workers are using newer screening pulmonary function tests to detect asymptomatic persons with early disease that still may be reversible. These results suggest that airway obstruction can be detected before it causes symptoms, and also that it is possible to differentiate one type of airway obstruction from another.

Even when the usual tests of pulmonary function are normal, airway obstruction can be detected by an abnormal decrease in maximal airflow rates, especially at low lung volumes. The association of a decreased single-breath CO diffus-